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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11, 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-11 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-11 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☒ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40512

1. Detailed Office Action

2. Formal Matters

2a. There are 11 claims of record, wherein Claims 1-10 are directed to products and/or composition, and claim 11 is directed to a method of treatment. While claim 11 can be properly restricted from claims 1-10, after consideration, no restriction will be imposed. Thus, this office action (O.A.) is directed to the merits of all of the claims of record 1-11.

2b. The specification is objected to in the numbering of the examples, which should be consecutive. Examples 1-8 are listed, then Examples 1-4 are listed starting at page 36. Correction is required

2c. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

2d. The Sequence Listing disk contained minor errors that have been corrected by STIC, and as a result the application is in compliance with the Sequence Rules.

2e. The title of the invention is not descriptive. A new title is required that is clearly indicative of the precise invention to which the claims are directed. The following title or the like is suggested that defines the specific osteoclastgenic agent: "IL-18 AS AN OSTEOCLASTGENIC INHIBITORY AGENT"

3. Objections and 35 USC 101 and 112 Rejections:

3a. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for a number of reasons.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "includes" in claims 2-4, and 6 appears to be used by the claim to mean "the identifying characteristic of the Il-18 in the form of the amino acid sequence," while the accepted meaning of "includes" is "an additional embodiment/feature." In the manner in which applicants have used this term does not constitute an additional embodiment/feature, but rather is the most identifying and inherent feature of the protein. Therefore, it is suggested that the claims be amended to use the more conventional language of "comprising". The following is suggested: "....wherein said IL-18 consist of or comprise the amino acid of ....."

Claims 2-4 and 6 are confusing in the use of "and" when used to refer to the Seq. ID. It is not clear if applicants intend for the inhibitory agent to be defined by any one of Seq. ID; or if the agent comprises all of the listed Sequence Identifier? If the former is contemplated, then the claims are objected to for failing to write proper Markush language for the alternative embodiments. [See MPEP 2173.05(h)]. If, however, the latter is contemplated, then it is not clear if these various sequences are contiguous or in tandem, and if these partial amino acid sequences constitute the entire/total sequence for the inhibitory agent. Correction and/or clarification are requested.

The claims are also indefinite and confusing in referring to the protein product with the Sequence Identifiers in conjunction with the phrase "as partial amino acid sequences". It is not clear if applicants contemplate a full length protein which comprises the partial sequence as well as other amino acid residues an embodiment, or if the claim is limited to an IL-18 protein product that is restricted to the amino acid residues of the Seq. ID. This is further complicated by the claim's use of "includes". However, it is not clear if the phrase "as partial amino acid sequences" is merely an adjective to define the Sequence Identifiers. Therefore, clarification and correction is requested. Furthermore, the use of "as partial amino acid sequence" cause the claim to be redundant, because it is inherently clear from the Sequence Identifiers that they are partial

sequences. It is suggested that this be deleted from the claims. If, however, applicants desire to have this descriptive in the claim, the following suggest is offered that would make the claim clear and consistent with more conventional claim language: ".....wherein the interleukin-18 consist of the partial amino acid sequence of SEQ ID NO: ....." Note that the suggested claims uses the term "consisting of" rather than the use of "comprising", because the latter term is "open-ended" and subject to encompass the entire full length amino acid sequence for the protein (See the prior art rejects below).

Claims 8-10 are indefinite and incomplete for failing to be consistent in the preamble and the body of the claim for claimed agent. The preamble of the claim appears to refer to an inhibitory agent, but the body of the claim appears to suggest a composition because of the presence of the other embodiments. Since some of the claims, namely claims 1-7 appear to suggest that the therapeutic agent is a single product, claims 8-10 appear to suggest that the therapeutic agent is in the format of a composition. Since the claims should use terms in a consistent manner, it is suggested that claims 1-8 be amended to delete reference to agent and merely refer to the IL-18 protein "osteoclastgenic inhibitor" rather than an agent since no other embodiment are listed. Likewise, it is suggested that claims 8-10 be amended to refer to "An osteoclastgenic composition comprising". Although applicants can be their own lexicographer, this is acceptable when the term is not used in a manner contradictory to that known in the art. Applicant's use of "agent" and their intended scope of such, as discussed at page 10 of the specification is not conventional. Amending the claims as suggested would obviate these aspects of the rejection. In a manner similar to the above, claims 8-9 are indefinite for failing to use proper Markush language to define the alternative embodiments for the additional agents that make up the other alternative embodiments of what appears to be an intended composition claims.

Claim 11 is somewhat confusing in line 5 for the use of "for". It would appear that this should be "from". Clarification or correction is requested.

3b. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some osteoclast-related diseases, does not reasonably provide enablement for the aspect of "preventing", nor is there enablement for treating or preventing the full scope of "osteoclast-related diseases". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use with a reasonable expectation of success the invention commensurate in scope with these claims.

The claim is non-enabling for the limitation of "preventing" osteoclast-related disease. The results of record have not established that any of the related diseases can be prevented. All that has been shown is that certain disease that are related to osteoclast can be treated. Prevention would necessarily mean that a patient that would be pre-dispose to having these disease be (if however this can be determined) give the Il-18 and that such administration would ensure that the patient did not develop these disease. Since prevention has not been shown, it is suggested that this limitation be deleted from the claim.

The claim is further non-enabling the treatment of any and all "osteoclast-**related** diseases", because the scope of such is not clear. The phrase "related" also renders the claim(s) indefinite as well as non-enabling because the claim includes elements not actually disclosed (those encompassed by "related"), thereby rendering the scope of the claim unascertainable-in a manner similar to "or the like" as discussed at MPEP § 2173.05(d). There is insufficient description and enablement in the specification for how "related" the disease would have to be to osteoclast?

3c) Claims 1, 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for IL-18 having the full length or certain partial sequences and

to methods of treatment using such, does not reasonably provide enablement for (a) any osteoclastgenic inhibitor of unspecific characterization that is merely referred by the name, as in claim 1, or for peptides from any specie form of the IL-18; (b) there is insufficient enablement for any "functional equivalent"; c) and there is insufficient enablement for the treatment of the broad array of osteoclast-related disease with the various small peptides of the claims, nor is there enablement for preventing any of the myriad of diseases (as stated above). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims make and use with a reasonable expectation of success.

The are various issues to this scope rejection - as the specification has not provided enablement that would be commensurate in scope with the breadth of the claims.

First of all, the specification is not enabling for a therapeutic protein product that is merely For example, claim 1 fails to set forth any physical characteristics (MW and how it is determine, the amino acid composition or sequence, pI, or other finger-printing characteristics), or specific or non-specific functional/biological activity. A name or an abbreviation is arbitrarily assigned by the researcher who isolates or discovers the protein based on the activity they have associated with it, however, as is the case with most proteins, there are generally many activities associated with a protein, and any one scientist will assign a name to a protein based on the particular activity that they are researching. This often leads to confusion in the art about what protein is actually being referred to as compared to other proteins with the same physical features, and it also results in any one protein being given/assigned different or multiple names, even though the resulting protein per se is the same despite the various names assigned to it. This is especially true for new and novel proteins, because names are subject to change, as has been the case for many protein, especially for many of the cytokines (note that the instant protein is known as IL-18, IGIF, IL-1γ, etc). Therefore, a name, without any identifying characteristics, does not serve to sufficiently distinguish or define the features of a protein so as to enable the skilled artisan to know what is

encompassed and intended by such in order to practice the claimed invention. This is further complicated by the fact that there are often multiple or variant forms of a protein, such that without specifically define characteristics, the skilled artisan would not know how to obtain the proper protein or peptide. The only other limitation recited by claim 1 is that the protein product is an "osteoclastgenic inhibitory agent", but this also fails to sufficiently characterize and enable the scope of the claim.

Furthermore, the specification is only enabling for peptides from the human IL-18. In the absence of sufficient examples, evidence of guidance, the specificating has not enabled the full length protein or peptides from all specie form of the protein, especially if since some of the claims fail to recite any physical or functional characterization.

The specification has enabled the preparation of both human and mouse IL-18, and the peptides of Seq. ID No's. 1-5 represent consensus peptides between these two specie forms of the IL-18 even though the amino acid residue numbering as compared to the wild-type IL-18 differs between human and mouse IL-18. Beyond this, there is no enablement for any other specie form of IL-18, nor is there sufficient guidance or evidence that the small peptides contemplated by the claims appear in all other specie forms of the IL-18. Thus, the claims which fail to refer to a specific sequence are not enabled for all specie forms or peptides for the various specie forms of IL-18.

At pages 4-5, 14 and 16, applicants discuss functional equivalent, but this represents a mere discuss of what applicants contemplate for the scope of the claims. However, this does not serve to enable the scope of the claims. First of all, the claims are written in such a way that they do not make clear or enable the kind of functional activity contemplated. Since most interleukins are pleiotropic in nature, and in the absence of the specification to provide structure-function studies for identifying regions on the protein that correspond to certain function or characteristics of the protein/peptide, there is insufficient enablement for the scope of functional equivalents.

The last issue for the lack of enablement of these claims is directed to the osteoclastgenic activity of the protein/polypeptides. The claims are written in such a way that it implies that the polypeptides of the Seq. ID possess this activity, however, the results in Tables 2-4 at pages 26-35 of the specification have been limited to the full length wild-type human and murine IL-18. As stated above, these peptide represent consensus peptides between human and murine IL-18, but the results of record have not clearly enabled peptides and methods of treatment that possess this activity. In a similar manner, claim 11 is broadly directed the treatment and prevention of osteoclast-related disease. First of all, it is not clear what the scope of these diseases are, nor how related the disorder must be that is encompassed by this term. In the absence of sufficient examples, evidence or guidance, the skilled artisan would be faced with undue experimentation for practicing the scope of the claims. The nexus between all diseases within the scope of the claims is not clear; it is not evident that these consensus peptides contribute to other osteoclastgenic activity; nor is it evident that all such diseases can be treated and/or prevent in the same manner; or if the treatment or prevention for any on disease would be predictive of that for the other diseases.

3d) 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter as written the claims read on products of nature despite the description that the protein is "an osteoclastgenic agent". The recitation of such things as "isolated" or reciting some level of purity or other descriptive which would distinguish the claims from products of nature would obviate this rejection.

4. Prior Art Rejection:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4a) Claims 1, 7-10, and claims 2-6 are rejected under 35 U.S.C. 102() as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ushio et al, Okamura et al (`324) Sana et a (`468)l.

Each of the prior art disclose a protein that is now known as IL-18, and that has the same sequence as that recited in the claims or is considered inherent. (See entire documents of each and claims). While each of the prior art do not state that the protein is an osteoclastgenic

inhibitor, that is a functional/biological property that represents further characterization of a known protein and which is inherent to the protein. Thus, the burden is upon applicants to establish a patentable difference. (In re Best 195 US PQ 430; and In re Swinehart 165 USPQ 226). Furthermore, the claims use open-ended language the define the claimed invention, thus they read on the entire protein (see claims 2-6).

4b. Claim 1 and 7-11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Udazgawa et al (J. Exp Med/1995).

These claims are being rejected based on the limitation of the claims for "functional equivalent" . The prior art teach that IL-6 possess osteoclastgenic inhibitory activity, and therefore reasonably appear to met the limitations of the claims, because the claims do not state that the functional equivalent has to be a portion of the IL-18 protei (see the entire document).

4c. Claims 1 and 7-11 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Udagawa et al (J Exp Med/1997) or Martin et al.

Each of the art teach that Il-18 has osteoclastgenic activity, and therefore meet the limitation of the claims (see entire documents of each). With regard to this particular rejection, it is pointed out that the authorship and inventorship differs, and Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The other art on the 892 is cited as of interest. Note that various of the art show that peptide regions of the various Seq ID overlap with peptide regions on other proteins that are distinct from the IL-18 protein.

6. ***Advisory Information:***

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1647, whose telephone number is (703)**

308-4232. Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800